

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Applicants sincerely thank the Examiner and her supervisor for holding a personal interview with Applicants' representative on October 1, 2007. The kind suggestions made by the Examiner and her supervisor have been incorporated into this reply.

I. CLAIM STATUS & AMENDMENTS

Claims 1-10 were pending in this application when last examined.

Claims 3 and 4 were examined and stand rejected.

Claims 1, 2 and 5-10 were withdrawn as non-elected subject matter.

Claims 3 and 4 are amended to recite "consists of" instead of "comprises".

No new matter has been added.

Applicants further note that Claim 3 and 4 were previously amended in the reply filed March 6, 2007 to recite the term "optionally". During the personal interview, the Examiner and her supervisor noted that such an amendment may not be supported. Applicants note that such term is inherently supported by the original claim language. In particular, the original claims called for administering the compound itself or a composition containing the compound and a carrier. Thus, claims 3 and 4 have merely been simplified by stating that the compound and "optionally" a carrier is administered. Applicants therefore suggest these claim amendments are supported by the claims as filed.

II. ANTICIPATION/OBVIOUSNESS REJECTION

On page 2, claims 3 and 4 were again rejected under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over US 5,143,935.

Applicants respectfully traverse this rejection, as applied to the amended claims, for reasons of record and for the following reasons.

1. The '935 patent fails to teach or suggest the compound of the amended claims as such reference only teaches racemic mixtures and does not enable the claimed stereoisomer

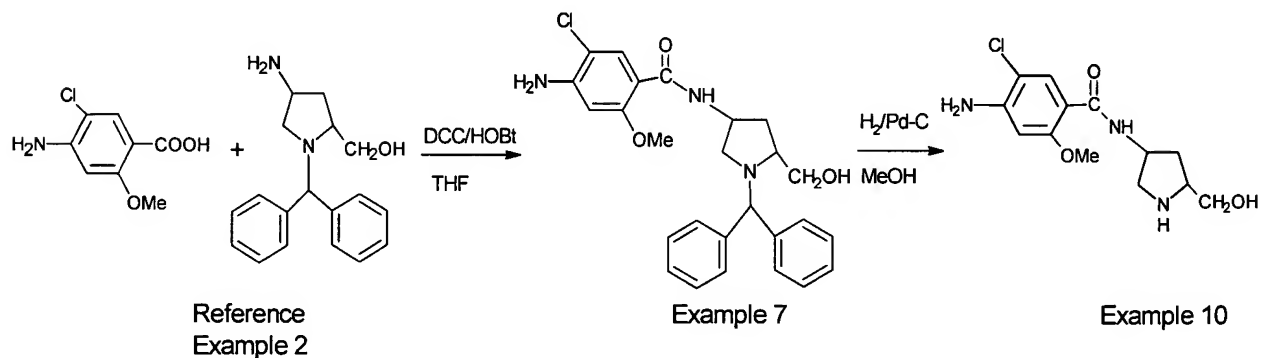
A. The '935 patent fails to specifically teach the compound of the amended claim

Claims 3 and 4 have been amended to recite “consists of” instead of “comprises” and therefore only include within their scope the particular stereoisomer claimed. On the other hand, the '935 patent only specifically teaches a racemic mixture.

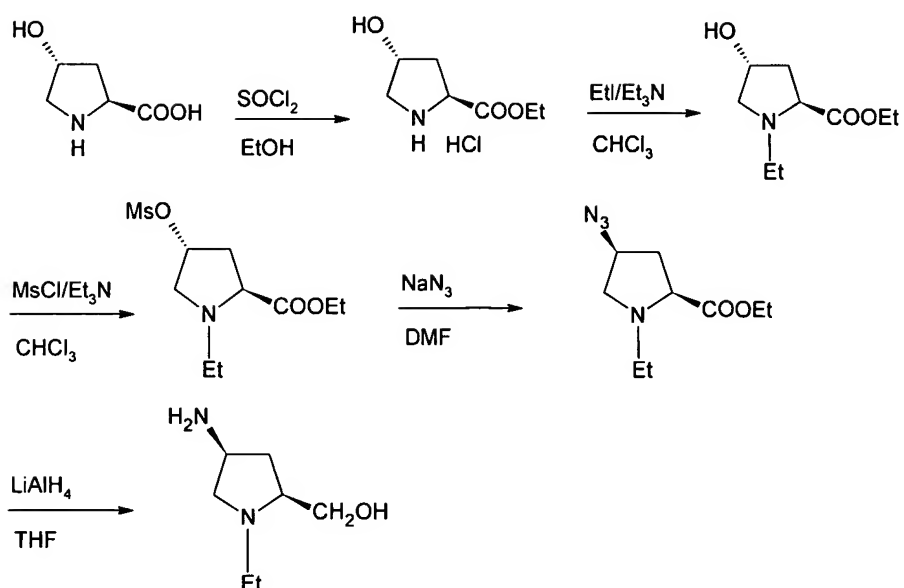
B. The '935 patent fails to teach how to isolate the claimed compound

As shown below, the compound of Example 10 of US 5,143,935 was synthesized by subjecting the compound of Example 7 to hydrogenation in the presence of Pd/C to replace diphenylmethyl on the ring-constituting nitrogen atom with hydrogen. That is, a racemic modification (racemate) was obtained by removing a diphenylmethyl group as the protective group contained in the compound of Example 7. Please note that the configuration of the compound of Example 7 was previously unknown.

Thus, the configuration of Reference Example 2 as the starting compound is an important factor determining the configuration of the desired synthesized compound.

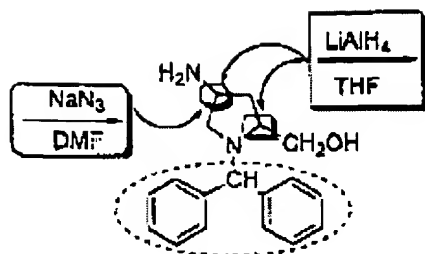


On the other hand, TKS159, which is one of four kinds of stereoisomers, was synthesized as shown below.



In particular, an ethyl group was introduced to a ring-constituting nitrogen atom by the 2nd step. In the final reduction reaction by LiAlH_4 of the N-ethyl-azido-ethoxycarbonyl pyrrolidine derivative, the configuration at the 2- and 4-positions of the desired compound was successfully preserved. However, the preservation of the configuration was accomplished based on the ring-constituting nitrogen atom substituted by an ethyl group.

On the other hand, as shown below, a person skilled in the art understands that where the substituent on the ring-constituting nitrogen atom is a diphenylmethyl group, the configuration at the 2- and 4-positions of the desired compound cannot be expected to be preserved because of steric hindrance and electronic effect. Further, stereoselectivity of an azide group at the 4-position of the pyrrolidine is influenced, and the preservation of the configuration cannot be controlled in the reduction reaction to obtain a pyrrolidine containing amino at the 4-position, hydroxymethyl at the 2-position and diphenylmethyl on the ring-constituting nitrogen atom.



Accordingly, the desired compound obtained from the compound of Example 7 is a racemate.

C. The Applicants intensively studied in order to isolate the claimed stereoisomer by a new synthetic method and therefore it would have required undue experimentation to isolate the claimed compound from the teachings of the '935 patent

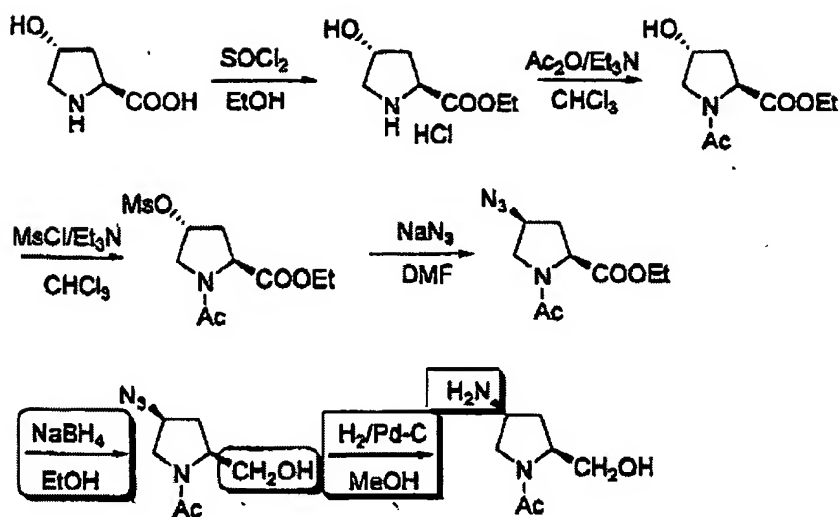
In the present invention, stereospecific synthesis via the following route was performed to avoid the above noted problems.

The stereospecific synthesis is characterized by the following:

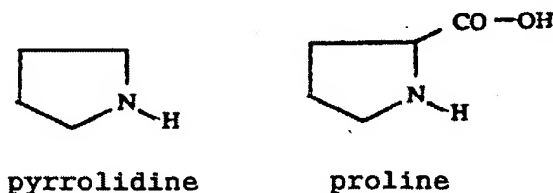
1) An acetyl group, instead of an ethyl group, was introduced to the ring-constituting nitrogen atom. Please note that an acetyl group is as large as an ethyl group but the introduction of an acetyl group resolved another problem. The problem is that in the reduction reaction by LiAlH₄ of the N-acetyl-4-azido-2-carboethoxy-pyrrolidine derivative, the N-acetyl group was eliminated from the ring-constituting nitrogen atom, so that the object N-acetyl derivative was not obtained.

2) The present inventors have intensively studied to obtain an N-acetyl derivative. As a result, the inventors found a new synthetic method. That is, the reduction reaction is conducted by two steps: (1) the reduction of ethoxycarbonyl to hydroxymethyl by NaBH₄ in EtOH, and then (2) catalytic hydrogenation of azido by Pd-C in MeOH. By adopting this method, the desired product containing an N-acetyl group was obtained.

Thus, by choosing an ethyl group and by using the combination of two kinds of reduction reaction, *i.e.*, (1) NaBH₄ in EtOH and (2) catalytic hydrogenation by Pd-C in MeOH, the desired compound, TM161 containing an N-acetyl group, was finally obtained. This synthesis method is shown below.



For your reference, the structures of pyrrolidine and proline are shown below.



Thus, applicants submit that since they had to develop a new synthetic method by intensive study in order to obtain the claimed stereoisomer, a skilled artisan would be required to engage in undue experimentation in order to obtain the claimed stereoisomer based on the '935 patent.

D. A skilled artisan could not have isolated the claimed compound at the time of filing based on the knowledge in the art without undue experimentation

There are many books describing how to handle an optically active compound, *e.g.* Enantiomers, Racemates and Resolutions, Samuel H. Wilen, Krieger Publishing Company, 1981. However, production of the claimed stereoisomer has not been previously described. In particular, production of hydroxyproline derivatives themselves have been described but production of the compound of the present invention, which contains an N-acetyl group, a hydroxymethyl group at the 2-position, and an amino group at the 4-position has not been described. For example, please see Journal of Organic Chemistry,

Vol. 46, page 2954 (1981) and Journal of the American Chemistry Society, Vol. 79, page 185 (1957).

During the personal interview with the Examiner and her supervisor, it was noted that the claimed stereoisomer might be isolated by crystallization, chromatography or other isolation methods. However, conventional crystallization is conducted by salt formation of a carboxylic acid moiety at the 2-position, which is one of the important functional groups in proline derivatives with chiral amines. This method is not feasible for production of the claimed compound, which contains only a hydroxymethyl group at the 2-position.

Further, purification/isolation by chromatography of the claimed compound may be possible depending upon the kind of compounds, but it is impossible to predict *a priori* the necessary procedure. Further, purification/isolation by chromatography can only be performed by intensive trial and error and the present inventors did not have knowledge that chromatography can apply to the compound of the present invention at the time of filing this application. Thus, obtaining the claimed compound by this methodology requires undue experimentation.

Therefore, at the time of filing of the present application, it was not known how to isolate the claimed stereoisomer. Further, at the time of filing of the present application, isolating the claimed stereoisomer would have required undue experimentation.

E. '935 patent fails to teach or suggest the claimed invention

Thus, Applicants submit (1) the '935 patent does not specifically teach the claimed stereoisomer; (2) the '935 patent does not teach a method for isolating the claimed stereoisomer and (3) a person of skill in the art at the time of filing would not have been able to isolate the claimed stereoisomer without undue experimentation. Thus, the '935 patent fails to teach or suggest the stereoisomer of the amended claims because this reference does not provide an enabling disclosure for producing only the claimed stereoisomer and a person of skill in the art at the time of filing of this specification could not determine how to isolate the claimed stereoisomer without undue experimentation. Please see MPEP 2121.02 and Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc., 501 F.3d 1263, (C.A. Fed. (Del.) September 5, 2007).

2. The claimed invention, as amended, exhibits unexpected effects and thus the '935 patent does not suggest the claimed invention

The present invention is characterized by administering 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide or an acid addition salt thereof. This stereoisomer has high binding affinity for serotonin receptor 4 (5HT₄) and does not cause thrombus formation, arteritis or encephalomalacia. Administration of this stereoisomer improves the movement of the digestive tract.

US Patent 5,143,935 and JP-A-17434/1993 describe that 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide (TKS159), or an acid addition salt thereof, improves the movement of the digestive tract. However, disorders such as thrombus formation, arteritis or encephalomalacia were observed when TKS159 was repeatedly orally administered to a beagle dog during safety testing.

On the other hand, the claimed stereoisomer (TM161) is a metabolite of TKS159 in a beagle dog and unexpectedly does not cause thrombus formation, arteritis or encephalomalacia, and is unexpectedly highly effective in improving the movement of the digestive tract. Thus, the cited art does not suggest the claimed invention because it does not suggest that the claimed stereoisomer has these unexpected properties.

The following experimental data showing that 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide hydrochloride (TM161) shows excellent effect as compared with TKS159.

A. The action of promoting the movement of the digestive tract

(1) Affinity for serotonin receptor 4 (5HT₄)

Test drugs	IC ₅₀ μM
TM161	0.25
TKS159	0.45

These results indicate that the affinity for serotonin receptor 4 of TM161 is 1.8 times greater than that of TKS159.

(2) Relaxation reaction in rat-extracted sample

Test drugs	IC ₅₀ μ M
TM161	0.7
TKS159	1.1

These results indicate that the relaxation reaction to TM161 in rat-extracted sample is 1.6 times greater than for TKS159.

Thus, applicants submit that it is apparent to a skilled artisan that TM161 is surprisingly and unexpectedly more effective in promoting movement of the digestive tract than TKS159.

B. Side-effects

The binding affinity for TM161 and TKS159 for the dopamine D2 receptor

Test drugs	IC ₅₀ μ M
TM161	34
TKS159	3.8

These results indicate that the binding affinity of TM161 is 8.9 times greater than that of TKS159. Binding with dopamine D2 receptor is a cause of side-effects, such as extrapyramidal sign.

C. Safety

TM161 was administered orally to three beagle dogs at a dose of 100 mg/kg once a day for 4 weeks.

Pathohistological tests were performed using a light microscope and abnormalities were not found. Further, neither thrombus formation, arteritis nor encephalomalacia was identified.

On the other hand, TKS159 was administered orally to three beagle dogs at a dose of 30 mg/kg once a day for 4 weeks.

Pathohistological tests were performed using a light microscope and abnormalities were not found. Further, neither thrombus formation, arteritis nor encephalomalacia was identified.

Applicants therefore note that TM161 can be administered in a 3.3 times larger dose than TKS159 without engendering side effects.

D. Conclusion

Thus, applicants submit that the '935 patent fails to suggest the claimed invention because it fails to teach the above noted unexpected effects. Applicants further note that, as indicated in part 1 above, this reference fails to teach the claimed invention and therefore cannot inherently teach such unexpected effects.

Applicants therefore suggest that, for the above noted reasons, this rejection, as applied to the amended claims, is untenable and should be withdrawn.

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,
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